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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/525,797	03/15/2000	Athanasius A Anagnostou	5218-39B	9917

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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	
MAIL DATE	**DELIVERY MODE**
11/16/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/525,797	ANAGNOSTOU ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *16 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *12,19-21,24-26 and 31-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *3,12,19-21,24-26 and 31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/16/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after allowance. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid and the petition for Withdrawal from Issue has been granted, since Applicant has submitted an IDS, filed on October 16, 2007, which is acknowledged and has been entered, an action on the RCE follows. Claims 12, 19-21, 24-26, 31-35 are currently pending and under consideration.

New Grounds of Rejection

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

"The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention."

3. Claims 12, 19-21, 24-26, 31-35 are rejected under 35 U.S.C. 112, first paragraph because the specification, while being enabling for a method of treating a solid, vascularized tumor with a chemotherapeutic agent, cisplatin (CIS), carboplatin, mitomycin does not reasonably provide enablement for a method of treating a solid vascularized tumor comprising administering erythropoietin (EPO), in an amount effective to enhance suppression of endothelial growth associated with administration or cisplatin, carboplatin, mitomycin, in a dosage range of 750 U/kg to 2000 U/kg prior to administering cisplatin, carboplatin or mitomycin. The specification does not enable any person skilled in the art to which it pertains, or

with which it is most nearly connected, to use the invention commensurate in scope with these claims. .

The claims are drawn to a method of treating a solid vascularized tumor comprising administering erythropoietin (EPO), in an amount effective to enhance suppression of endothelial growth associated with administration or cisplatin, carboplatin, mitomycin, in a dosage range of 750 U/kg to 2000 U/kg prior to administering cisplatin, carboplatin or mitomycin.

The specification exemplifies, in example 5, the *in vitro* effect of EPO administration, followed two hours later by CIS, upon endothelial cells grown in culture wherein cell proliferation and viability were decreased by as much as 81% compared to controls, wherein the inhibition was dose dependent, compared to controls (see pages 18-19).

One cannot extrapolate the teaching of the specification to the scope of the claims because (a) the art recognizes that the *in vitro* demonstration of decreased endothelial cell proliferation and viability cannot be reasonably or predictably extrapolated to *in vivo* treatment of solid vascularized tumor, (b) the art recognizes the unpredictability of the cancer drug therapeutic arts.

In particular, (a) one cannot extrapolate the teaching of the specification to the scope of the claims because the exemplification presented is not commensurate in scope with the claimed invention because the *in vitro* model is not drawn to a method of treating a solid vascularized tumor and in fact does not even include cancer cells in the assay. Further the art recognizes, that even if cancer cells were present in the system, that *in vitro* assays cannot duplicate the complex conditions of *in vivo* therapy. In the assays, the agents are in contact with cells during the entire exposure period. This is not the case *in vivo*, where exposure at the target

site may be delayed or inadequate. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful therapy. Thus the *in vitro* tests of record do not sufficiently duplicate the conditions which occur *in vivo* to predictably enable the claimed invention. Further, although drawn to assays which in fact include cancer cells, the teachings of Zips et al (In vivo, 2005, 19:1-7) are relevant to the instant claims. In particular Zips et al specifically teach that despite their importance for drug testing, *in vitro* methods are beset by pitfalls and inherent limitations (p. 3, col 1). In particular the authors state that "It is obvious that cells in culture represent an artificial and simplified system. Unlike the situation *in vitro,* a tumor is a 3-dimensional complex consisting of interacting malignant and non-malignant cells. Therefore, prediction of drug effects in cancer patients based solely on *in vitro* data is not reliable and further evaluations in animal tumor systems is essential (p. 3, col 2). Thus, the art recognizes that the *in vitro* demonstration of decreased endothelial cell proliferation and viability cannot be predictably extrapolated to *in vivo* treatment of solid vascularized tumor.

In particular, (b) one cannot extrapolate the teaching of the specification to the scope of the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable. For example Gura, of record, teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence in

an appropriate animal model, with data commensurate in scope with the invention claimed, no one skilled in the art would accept the assertion that the claimed method would function as claimed based only upon the *in vitro* demonstration disclosed by Example 5 of the specification.

The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict that the invention would function as claimed with a reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to practice the claimed invention.

It is noted that although Applicant presents convincing objective evidence in (a) the Sigounas Declaration submitted July 15, 2003 that demonstrates that administration of 60 U/kg EPO to mice prior to administration of CIS resulted in effective therapeutic treatment of a solid vascularized tumor in an appropriate animal model, (b) the Sigounas Declaration submitted November 2, 2005 in combination with the Sigounas Declaration of November 30 2006 that demonstrates that administration of 60 U/kg EPO prior to administration of CIS, carboplatin or mitomycin resulted in effective therapeutic treatment of a solid vascularized tumor in an appropriate animal model, none of these declarations are commensurate in scope with the instantly claimed invention requiring a dosage in the range of 750 Unites per kilogram to 2000 Unites per kilogram EPO. In particular, in the Experimental Data (II) submitted in the Opposition to European patent No. 0 933 995, Annex 13, it is reported that female C57BL/6 mice – 6-8 weeks old and weighing 15-20 grams were used in the *in vivo* exemplification presented. It is noted that this Experimental Data is not relevant to the enablement

of the instant claims because it is not commensurate in scope with the instantly claimed invention since the animals did not present with tumor cells and thus were not an appropriate model of *in vivo* treatment of a solid vascularized tumor as instantly claimed. However, relevant to the instant rejection is the fact that the data presented in Experimental Data (I) submitted in the Opposition to European patent No. 0 933 995, Annex 12 appears to be identical to the data presented in the Sigournas Declaration submitted in the instant application on November 2, 2005, wherein female C57BL/6 (also 7-8 weeks old) mice were also used as the model.

Thus, it appears that the mice used in the Sigournas Declaration submitted November 2, 2005 (and incidentally used in both the Sigounas Declaration of November 30 2006 and the Sigounas Declaration submitted July 15, 2003) weigh 15-20 grams. Clearly, given that the mice weigh 15-20 grams, administering 60 U/kg to these mice would result in the administration of a dose of .9 U/kg and a dose of 1.2 U/kg EPO, respectively. This dose is clearly not within the range instantly claimed. Further, even if one were to find that a typographical error had occurred and that each mouse is administered 60 U of EPO, a dose of 750 U/kg would require the administration of a dose of 11.25 Units and a dose of 15 Units for mice 15 and 20 grams, respectively. In addition, a dose of 2000 U/kg would required the administration of a dose of 30 Units and a dose of 40 Units for mice 15 and 20 grams, respectively. Thus, even if a typographical error had occurred, the dose administered in the Declarations is well above that instantly claimed. Given the known unpredictability of the art, because the data presented in the Declarations is not commensurate in scope with the claimed invention, the Declarations do not enable the claimed invention. Submission of a Declaration

with objective evidence, demonstrating that the units administered per mouse are within the claimed range would obviate the instant rejection.

4. The IDS and papers submitted on October 16, 2007 have been carefully considered. Examiner has found that none of the references cited are prior art that read on the patentability of the instant claims. Further, the entire prosecution history of the instant application has been carefully reviewed and considered, resulting in the new grounds of rejection set forth above.

5. It is noted that although carefully considered, submitted Items 1-5, A1, A2, A9, A10, A12, A13 have been lined through in the IDS because these items do not appear to be published.

6. No claims allowed.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached at 571-272-0898. The fax phone number for this Art Unit is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

Susan Ungar
Primary Patent Examiner
November 7, 2007

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